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Cardiovascular consequences of obstructive sleep apnea in different study models and novel perspectives

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Abstract: PURPOSE OF REVIEW: Obstructive sleep apnea (OSA) is heterogeneous in terms of contributing pathophysiological mechanisms, clinical presentation, and consequences. Different study models from animal models of intermittent hypoxia over case-control, cohort, and population-based observational studies to uncontrolled interventional and randomized controlled interventional trials have contributed to the knowledge base. Controversial findings on underlying mechanisms and consequences of untreated OSA have challenged the field and resulted in uncertainty in treatment recommendations. RECENT FINDINGS: The heterogeneity of OSA in pathogenesis and clinical outcomes and strengths and limitations of different study models and designs used for studying OSA pathophysiology and cardiovascular consequences are discussed on the background of controversial findings on cardiovascular outcomes in OSA. In addition, recent findings from randomized controlled continuous positive airway pressure therapy withdrawal trials, an efficient and controlled study model, are highlighted. SUMMARY: Novel designs for clinical trials on long-term outcomes in the highly prevalent patient group with OSA addressing the heterogeneity in underlying mechanisms, different phenotypes in terms of cardiovascular risk, and new treatment concepts are needed to improve clinical practice standards.

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Cardiovascular consequences of obstructive sleep apnea in different study models and novel perspectives

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Obstructive sleep apnea (OSA) is heterogeneous in terms of contributing pathophysiological mechanisms, clinical presentation, and consequences. Different study models from animal models of intermittent hypoxia over case-control, cohort, and population-based observational studies to uncontrolled interventional and randomized controlled interventional trials have contributed to the knowledge base. Controversial findings on underlying mechanisms and consequences of untreated OSA have challenged the field and resulted in uncertainty in treatment recommendations.

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Novel designs for clinical trials on long-term outcomes in the highly prevalent patient group with OSA addressing the heterogeneity in underlying mechanisms, different phenotypes in terms of cardiovascular risk, and new treatment concepts are needed to improve clinical practice standards.

Keywords
continuous positive airway pressure, hypertension, intermittent hypoxia, obstructive sleep apnea, randomized controlled trial

INTRODUCTION

The underlying mechanisms and pathophysiological consequences of obstructive sleep apnea (OSA) have been well described since its recognition as a specific sleep-related breathing disorder in the 1970s. The cardiovascular consequences of OSA were recognized early in the history of OSA [1], yet there are still several uncertainties and controversial findings in this field, especially on the effects of treatment of OSA on cardiovascular outcomes. The controversial findings might be explained by having studied a heterogenous population with differences in contributing pathomechanisms and pathophysiological consequences of OSA and by using different study designs and models. In addition, the difficulty in performing randomized controlled continuous positive airway pressure (CPAP) trials on long-term cardiovascular outcomes in both symptomatic (unethical of withholding an effective treatment) and asymptomatic patients (insufficient treatment adherence, potentially not at risk for an OSA-associated adverse cardiovascular outcome) with OSA has challenged the field.

OSA is a heterogeneous disease not only in symptom burden and cardiovascular and metabolic consequences but also in the underlying

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KEY POINTS

- Inconsistent findings on pathophysiological mechanisms and long-term consequences of OSA have challenged treatment concepts for patients with OSA.
- Different study models (cell culture and animal models of intermittent hypoxia, case control studies, cohort studies, populational-based observational studies, uncontrolled interventional trials, randomized controlled trials) have been used to study underlying mechanisms and consequences of OSA, each design having its advantages and limitations.
- Short-term CPAP withdrawal in previously highly compliant patients is an effective way to study the pathophysiological consequences of OSA and differences between baseline and follow-up can be attributed to OSA recurrence.
- OSA is a heterogeneous disease in terms of underlying mechanisms, symptom burden, and cardiovascular consequences.
- Addressing prognostically relevant phenotypes and incorporating novel treatment options in well designed trials will provide new knowledge to guide treatment recommendations for patients with OSA.

pathophysiology. Contributing factors such as upper airway anatomy and function, lung mechanics, respiratory control, and arousal threshold may vary considerably between individuals with OSA. Characteristics like obesity or sex and comorbidities play an important role in both the pathogenesis and sequelae of OSA, and are therefore relevant for the clinical impact of OSA and treatment recommendations. In addition, the metabolic and cardiovascular consequences may differ considerably between symptomatic and asymptomatic patients with OSA, and between those with or without a high hypoxic burden or pronounced sleep fragmentation. The recent identification of different phenotypes [2] and patient clusters [3–5], and the development of treatment alternatives to CPAP allow a more tailored treatment approach and advance personalized medicine in OSA as is the current concept in most chronic respiratory diseases.

This highlights the need for novel study designs using stratification by phenotypes, and the awareness of the strengths and limitations of currently used study models. The present review focuses on current models and trial designs to study the vascular and other pathophysiological consequences of OSA and treatment effects, and their limitations, and outlines the lessons learned from the CPAP withdrawal model, a specific study design to study the sequelae of OSA in an efficient and controlled way.

AVAILABLE APPROACHES TO STUDY THE PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNEA – OF MICE AND HUMAN; OF CASES, SNORERS AND CONTROLS; OF OBSERVING AND RANDOMIZING; OF INITIATING AND WITHDRAWING A TREATMENT

The pathophysiological consequences of OSA have been studied using different approaches – using cell culture and rodent models of intermittent hypoxia, simulated intermittent hypoxia in humans, case–control studies comparing patients with OSA to healthy controls and snorers, population-based epidemiological observational studies, cohort studies of OSA, uncontrolled interventional trials, and randomized controlled CPAP trials (Fig. 1). Because OSA can be effectively treated with CPAP, studying treatment effects provides knowledge on the reversible consequences of OSA.

Intermittent hypoxia has been most extensively studied as a direct pathophysiological mechanism in OSA and is considered the most important factor linking OSA with vascular damage. The effect of arousals and intrathoracic pressure swings has been studied as well [6–8]. Case–control and interventional CPAP trials assessing OSA as a disease – rather than looking at limited or simulated pathomechanisms of OSA – incorporate the risk of bias by confounding factors and pooling heterogenous patients with distinct contribution of the direct pathomechanisms. Epidemiological observational studies have generated hypotheses on cardiovascular consequences of OSA, however, do not allow the identification of a causal relationship between OSA and the observed changes in cross-sectional or longitudinal analyses [9–15]. Each model and study design has its benefits and limitations, and the current knowledge on the consequences of OSA is based on the combined evidence from experimental, observational, and interventional studies.

Animal models of intermittent hypoxia

Rodent models of intermittent hypoxia have contributed to the knowledge on pathophysiological consequences of OSA, especially the alterations of the cardiovascular system in chronic intermittent hypoxia studied in the absence of confounders [16,17]. Extent, duration and frequency of intermittent hypoxia play a role in the balance between maladaptive harm and adaptive beneficial mechanisms (e.g. preconditioning effects). In addition, the

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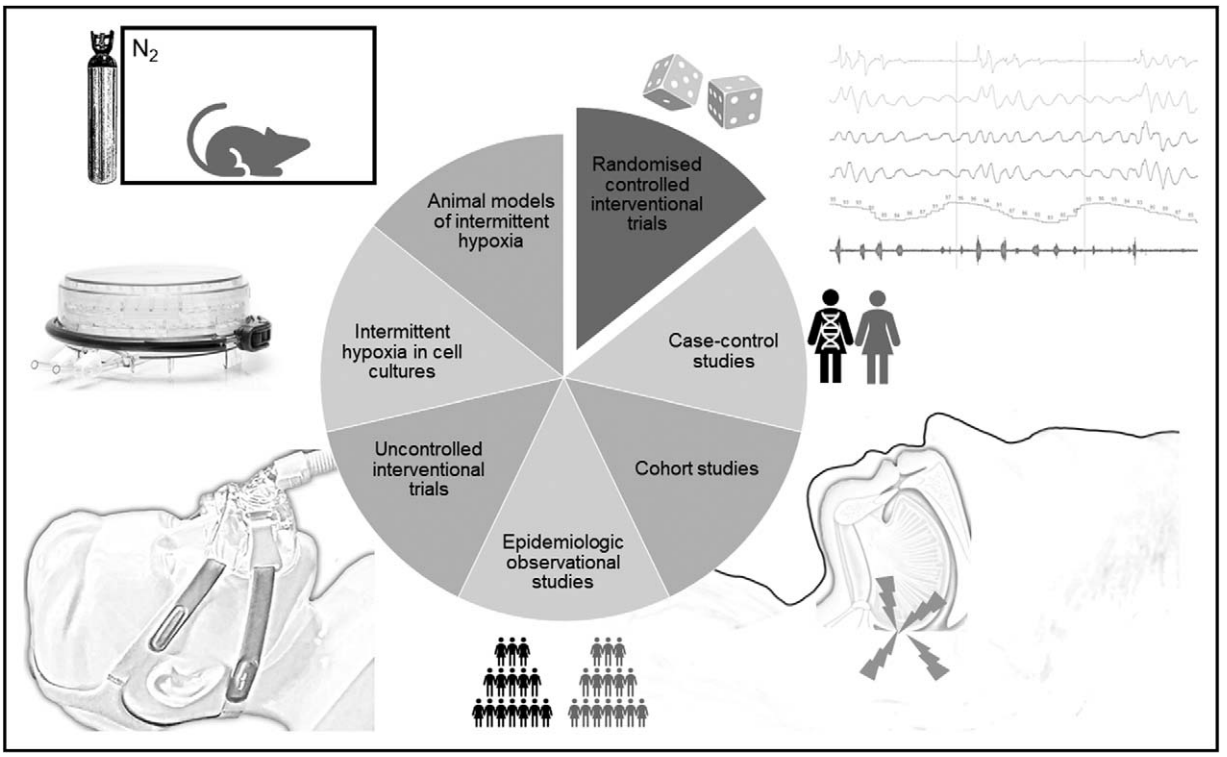

FIGURE 1. Different study models and design previously used to study pathophysiology and cardiovascular consequences of obstructive sleep apnea.

exact pattern of deoxygenation–reoxygenation and the vessel type or target organ studied might determine the beneficial versus harmful effects of intermittent hypoxia [18]. Experimental protocols and hypoxia paradigms differ between different rodent models and research groups [16,18], making comparison across studies and translating the findings to human OSA difficult. However, these animal models allow the identification of potential causality between experimental intermittent hypoxia and the outcome of interest. Important lessons on the complex effects of intermittent hypoxia, for example on increased sympathetic activity and blood pressure [19,20], on endothelial dysfunction [21], and on the role of adipose tissue for intermittent hypoxia-associated insulin resistance [22] have been learned from animal models.

The major limitations of these models are the difficulty of comparing the degree and pattern of exposure to experimental intermittent hypoxia to human OSA, and the usually isolated assessment of intermittent hypoxia excluding factors like potential hypercapnia, sleep fragmentation, intrathoracic pressure swings, and hemodynamic effects, which play an important role in the pathophysiological consequences of OSA [23,24]. However, the isolated assessment of intermittent hypoxia allows the better understanding of the contribution of specific direct mechanisms to intermediate consequences and vascular damage in OSA, which is important for identification of at-risk groups and for mechanism-targeted treatment.

Clinical trials including patients with obstructive sleep apnea

In patients with OSA, the way from case–control and cohort studies over uncontrolled interventional trials to randomized controlled CPAP trials and meta-analyses has led from hypothesis generating to establishing evidence for a causal relationship between OSA and hypertension.

Case–control studies comparing patients with OSA to snorers without OSA and/or healthy controls have suggested a high prevalence of hypertension in OSA and identified patient characteristics like male sex that strengthen this association [25,26]. However, case–control studies have important limitations (e.g. selection bias) that limit their validity.

Population-based observational studies such as the Wisconsin Sleep Cohort Study or the Sleep Heart Health Study have made important contributions to the knowledge on the cardiovascular consequences of OSA. In a longitudinal analysis, there was a dose–response relationship between OSA severity and incident hypertension at a follow-up of 4 years [27]. A cross-sectional analysis of the largest population-based study on this topic confirmed a strong

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association of OSA with hypertension in the subgroup with severe OSA only [9]. In addition, OSA has been associated with adverse cardiovascular outcome in population-based cohort and observational sleep clinic cohort studies [13,28–33]. These studies have indicated that the risk for cerebrovascular and cardiovascular events might only be elevated in moderate-to-severe or severe OSA but not in mild OSA. However, the association between OSA and cardiovascular disease is multifactorial and mediated by comorbidities and the typical clustering of cardiovascular risk factors in these patients, which are important confounders. Randomized controlled CPAP trials on cardiovascular outcomes are difficult to perform for several reasons, for example because of the problem of withholding an effective treatment to symptomatic patients over a prolonged period, selecting a population potentially not at risk for adverse outcome when including only asymptomatic patients, and the difficulty of achieving a sufficient treatment adherence to CPAP. If CPAP adherence is insufficient, the treatment effect is underestimated or completely vanishes. Ideally, patients use their CPAP every night for the whole night (6–8 h). However, nightly CPAP usage in previous large randomized controlled trials was typically 3–4 h with rare exceptions between 4 and 5 h [34–41].

Up to now there is only one published randomized controlled trial that has been powered to assess the effect of CPAP therapy on hard cardiovascular endpoints [35]. This trial has been well designed considering existing evidence for sample size estimation, trying to increase adherence by using a run-in CPAP period, and responsibility by excluding severely symptomatic patients but using sleepiness in minimization for random allocation to CPAP or usual care. This trial in middle-aged predominantly male Asians with established cardiovascular or cerebrovascular disease in not severely symptomatic patients with OSA (oxygen desaturation index 28/h in a level IV home sleep study, Epworth Sleepiness Scale 7.4) found no effect of CPAP therapy (mean usage 3.3 h/night) on secondary prevention of vascular death or hospitalization [35].

Other randomized controlled trials provided clear evidence for an independent association of OSA with hypertension and with endothelial dysfunction [42–44]. Considering all evidence from randomized controlled trials independent of the patient group studied, the blood pressure measure used, or treatment adherence, the overall blood pressure lowering effect of CPAP therapy is 2–3 mmHg. However, the effect size differs between blood pressure measures (mean 24-h-blood pressure vs night-time blood pressure versus office blood pressure versus home blood pressure) and between patient groups (no hypertension vs. hypertension versus resistant hypertension; sleepy vs. nonsleepy OSA; nonsevere vs. severe OSA). In addition, meta-analyses have also provided evidence for a significant association of the blood pressure lowering effect of CPAP and nightly CPAP usage [45]. In patients with resistant hypertension, the effect of CPAP on blood pressure was more than double (5–7 mmHg) compared with patients without resistant hypertension [46,47]. There is still a need for well designed randomized controlled trials in the research field of OSA to assess outcomes in different phenotypes and to evaluate treatment alternatives to CPAP. However, the time for classical randomized controlled trials simply randomizing everybody to the treatment or the control group seems to be over. Because of feasibility issues and the lessons we have learned from previous trials, such a trial design is unlikely to provide robust findings that influence clinical practice. Phenotyping and stratification and novel treatment concepts should be considered when designing future trials. In addition, if novel therapeutic devices are used, identification of responder and nonresponder criteria should be implemented into the trial design.

THE CONTINUOUS POSITIVE AIRWAY PRESSURE WITHDRAWAL MODEL TO STUDY THE PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNEA

To overcome some of the problems of conventional CPAP trials and to propose and efficient model to study the pathophysiological consequences in a controlled way, the CPAP withdrawal model was introduced [42]. The CPAP withdrawal model is an experimental protocol to investigate the pathophysiology of human OSA and to assess treatment effects of CPAP or novel therapeutic devices [48].

In a randomized controlled interventional trial design, patients with known OSA who are effectively treated (residual AHI < 5/h) and optimally adherent to CPAP (using it every night and all night) are randomized to either continue therapeutic CPAP (control group) or to withdraw it by the use of a subtherapeutic sham-device (intervention group) for a short period (Fig. 2). In most patients, a therapy withdrawal of several days results in recurrence of OSA and therefore allows studying the pathophysiological changes that can be attributed to OSA in a controlled model, avoiding many sources of bias of case–control studies or conventional CPAP-trials. Persistence and immediate recurrence of OSA is confirmed before study inclusion by home overnight pulse-oximetries off CPAP. After a minimum

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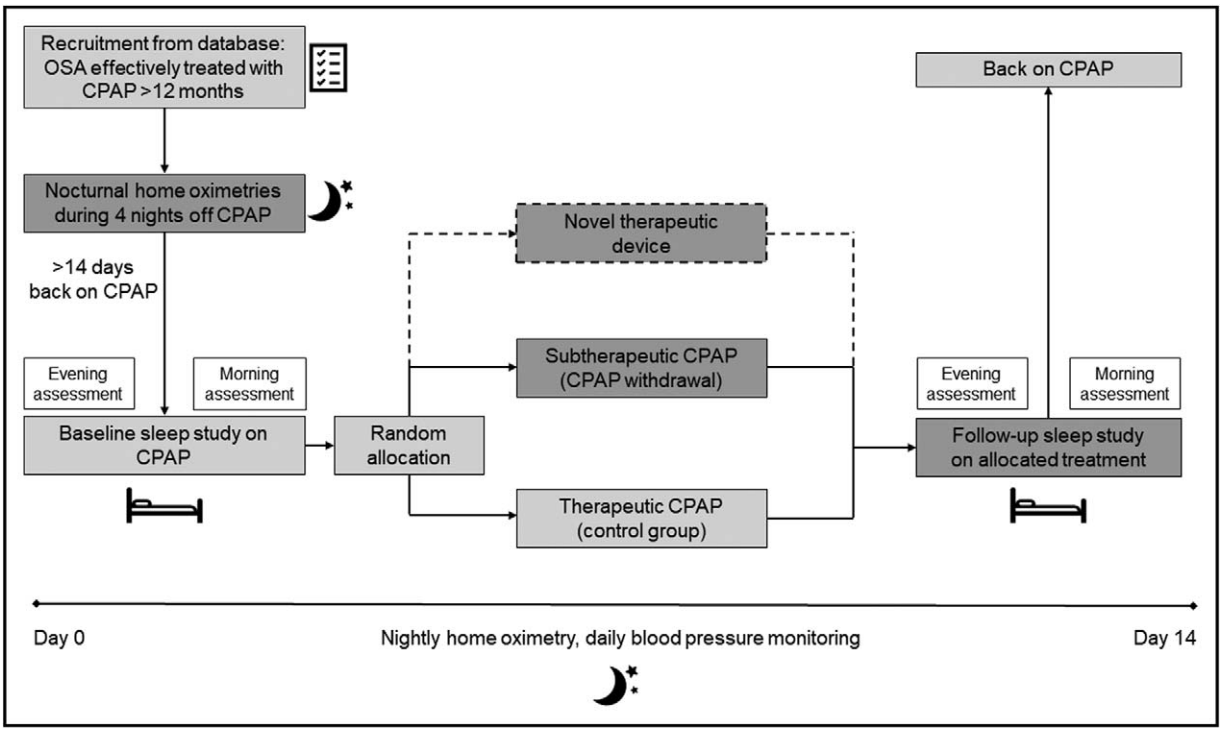

FIGURE 2. The CPAP therapy withdrawal model as it is used in randomized sham-controlled CPAP trials or with additional treatment arms to test a novel therapeutic device.

of 2 weeks being back on CPAP, patients have their baseline sleep study on CPAP and baseline assessments while being treated for OSA. The next morning, patients are randomized to the control or the withdrawal group and perform a nightly home oximetry during the intervention period that documents the recurrence pattern of OSA. The follow-up sleep study and assessments are performed 2 weeks after randomization on the allocated treatment (Fig. 2). Each patient in the withdrawal group serves as its own control at baseline, and the control group continuing therapeutic CPAP helps to avoid the typical bias of nonrandomized studies. Several of these randomized controlled CPAP withdrawal trials have been performed in the last years and gave insight into cardiovascular and metabolic consequences of OSA and recurrence patterns in response to an interruption of CPAP [42,43,49–52,53▪,54,55▪▪,56▪,57]. The model has also been used to assess the effect of other treatments than CPAP [58,59▪▪]. In addition, important lessons on night-to-night variability and sustained effects of OSA treatment have been learned [49,53▪].

Knowledge gained from continuous positive airway pressure withdrawal studies

These randomized controlled CPAP withdrawal trials have provided robust evidence on diverse cardiovascular and metabolic consequences of OSA [48]. Recurrence of OSA during a short-term CPAP therapy withdrawal was associated with a significant increase in urinary catecholamine as marker of increased sympathetic activity and a progressive decrease in peripheral endothelial function after 1 and 2 weeks when compared to the control group continuing CPAP [42,60]. Along with these changes, a clinically relevant increase in morning home and office systolic (+9 and +5 mmHg, respectively) and diastolic blood pressure (+7 and +5 mmHg, respectively) was found [43]. The observed change in blood pressure in untreated OSA in this group of patients with an optimal CPAP adherence was considerably larger than in conventional CPAP trials, in which CPAP usage is usually suboptimal and the treatment effect underestimated. A higher AHI, the use of more antihypertensive drugs, a lower blood pressure at baseline and the absence of statin usage were independent predictors of a pronounced increase in blood pressure in response to CPAP withdrawal. This highlights the role of OSA as a secondary cause of hypertension and the need for a combined treatment by antihypertensive drugs and CPAP in hypertensive patients with OSA. The findings led also to the speculation of a protective role of statins in OSA-induced endothelial dysfunction.

The heart and the brain are important target organs potentially being affected by the detrimental

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pathophysiological sequelae of OSA. In a randomized controlled CPAP withdrawal trial powered to detect a minimal clinically important difference in myocardial perfusion as assessed by the gold standard technique N^{13}-ammonia-positron emission tomography, OSA recurrence had no effect on myocardial perfusion and coronary endothelial function during daytime in patients with moderate or severe OSA despite a relevant increase in blood pressure and heart rate and the previously found peripheral endothelial dysfunction [51]. In line with the findings on myocardial perfusion, an additional randomized controlled trial studying cerebrovascular reactivity using functional magnetic resonance imaging measuring blood oxygen level-dependent response to breathing stimuli during daytime found no effect of OSA on cerebrovascular reactivity or cerebral blood flow [56▪]. However, despite preserved vascular function during daytime, the brain is exposed to OSA-induced changes during sleep that might explain neurocognitive dysfunction. Near infrared spectroscopy was used to monitor cerebral tissue oxygenation and hemoglobin concentration during in-hospital sleep studies in patients with moderate to severe OSA who were allocated to either withdraw CPAP or continue therapeutic CPAP [55▪▪]. OSA recurrence was associated with intermittent and sustained falls in cerebral tissue oxygenation during sleep of a clinically relevant degree, in some patients sufficient to cause cerebral ischemia associated with functional impairment.

Using the CPAP withdrawal model as human model of intermittent hypoxia, markers of oxidative stress were assessed in 59 patients with moderate or severe OSA at baseline and 2 weeks after randomization to either therapeutic or subtherapeutic CPAP. Contrary to the hypothesis, the return of intermittent hypoxia during CPAP withdrawal did not result in increased levels of markers of oxidative stress, for example early morning blood malondialdehyde [50]. OSA recurrence led to a significant reduction in urinary F2-isoprostane suggesting a reduction in oxidative stress. A possible explanation was a significant increase in the antioxidant superoxide dismutase, a marker of hypoxic preconditioning, that might prevent the damage of hypoxia-reoxygenation in intermittent hypoxia.

A recent randomized controlled cross-over trial studied the role of intermittent hypoxia on morning blood pressure by withdrawing both study arms from CPAP and randomizing them to either nocturnal supplemental oxygen or sham-oxygen (air) [59▪▪]. In this study design, a short-term CPAP withdrawal has been used as real-life model of intermittent hypoxia in OSA. Nocturnal supplemental oxygen abolished the rise in early morning blood pressure during CPAP withdrawal when compared to sham-oxygen. As supplemental oxygen attenuated the hypoxic dips without significantly affecting the apnea–hypopnea index or arousals, it was concluded that intermittent hypoxia is the dominant mechanism for the rise in morning blood pressure (and sympathetic activity) seen in patients with OSA [59▪▪]. This randomized controlled trial provides firm evidence for the mechanistic pathway 'intermittent hypoxia-sympathetic overshoot-increased blood pressure'.

The CPAP withdrawal model has also been used for a metabolomic study in OSA. Untargeted exhaled breath analysis was used to define the effect of OSA on the breath profile, which contains a wealth of metabolic information as volatile exhaled compounds that are released along the blood gas barrier. This study has shown that OSA is associated with a distinct breath pattern allowing differentiation between treated and untreated OSA with a high diagnostic accuracy [52]. OSA recurrence resulted in an increase in exhaled molecules associated with stress, altered lipid peroxidation and the gut flora metabolism [52].

Although a recurrence of OSA to some degree is typically seen in the majority of patients from the first nights on when CPAP is stopped – although usually of a lower severity compared to the time of the diagnosis, we found that about a third of an efficiently CPAP-treated OSA cohort does not experience a recurrence of OSA within four nights off CPAP withdrawal (during the pretrial screening [49]). This finding was not explained by a change in weight. These differences in recurrence may reflect different OSA phenotypes and indicate sustained effects of CPAP therapy. The underlying mechanisms remained speculative in this study. Upper airway function and edema and respiratory control are possible factors being influenced by long-standing CPAP therapy. Understanding why and how some have an immediate return of OSA and some have not will help to develop novel treatment strategies for patents with suboptimal and intermittent CPAP usage.

Nightly oximetry during the 2-week CPAP withdrawal revealed a high night-to-night variability of OSA severity according to the oxygen desaturation index (Fig. 3) in most patients. Shifts in OSA severity category between nights were found in 78% of patients. The variability was higher in less severe OSA [53▪]. This knowledge challenges the current practice of a single-night diagnostic sleep study and therapeutic recommendations based on conventional thresholds of apneas and hypopneas or cyclic oxygen desaturations per hour of sleep.

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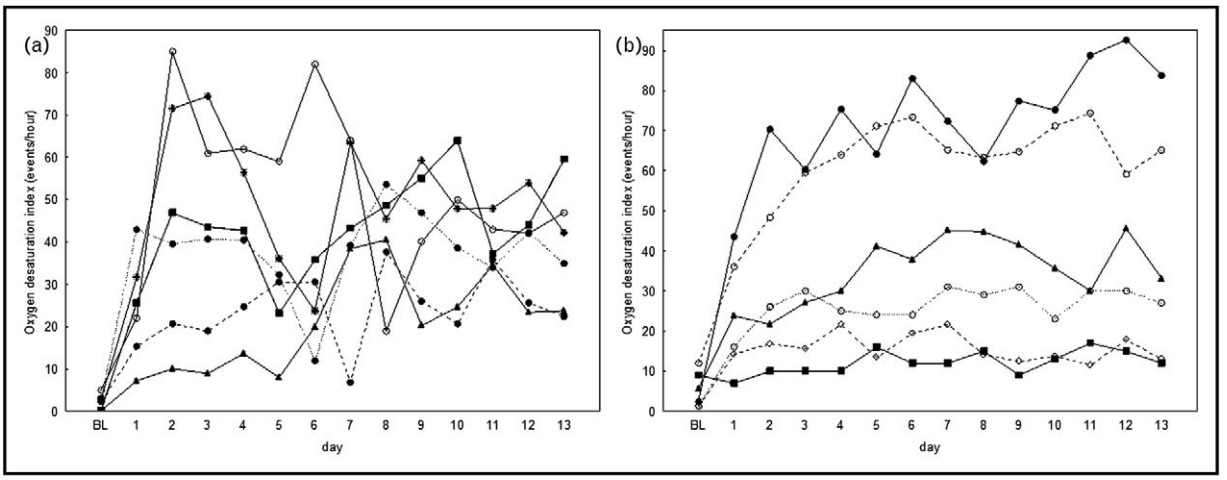

FIGURE 3. Course of 4%-oxygen-desaturation-index from baseline on CPAP (BL) over 13 nights of CPAP withdrawal in nocturnal home oximetry. (A) Six exemplary patients with a high night-to-night variability of OSA severity. (B) Six exemplary patients with a more stable pattern of OSA recurrence.

Its advantages and its limitations

The withdrawal model allows fast recruitment of well characterized patients and a limited intervention period, and estimation of a maximal treatment or withdrawal effect. The model avoids many sources of bias (e.g. by randomization, maximal treatment effect, no change of confounders like obesity in the short-term). However, the withdrawal model might also have a bias towards including patients with less severe OSA-related symptoms because they are more likely to temporarily stop CPAP. A major limitation is that the consequences of OSA recurrence during a short-term withdrawal of CPAP therapy might not necessarily be identical with long-term effects of untreated OSA.

IMPLICATIONS FOR FUTURE RESEARCH AND FUTURE TARGETS

It is unknown to which extent the changes observed in response to OSA recurrence during a 2-week CPAP therapy withdrawal can be translated to long-term consequences of OSA, and which adaptive mechanisms will be activated in the long term. Therefore, a planned study will use an adapted study design to allow comparison of pretreatment, changes upon CPAP therapy and withdrawal effects to compare acute, intermediate and chronic consequences of OSA on cardiovascular and metabolic outcomes. In other future randomized controlled CPAP withdrawal trials, the effect of OSA on the control of comorbidities, e.g. heart failure, will be assessed and novel therapeutic approaches tested in a head-to-head comparison with both CPAP and untreated OSA.

CONCLUSION

In summary, there are many different study models and designs available to study the pathophysiological consequences of OSA. Each model has its benefits and its limitations. The CPAP withdrawal model allows to study OSA pathophysiology and treatment alternatives to CPAP in a controlled way but has a limited comparability to long-term treatment effects of CPAP. Combining the strengths of different models in collaboration projects addressing the current needs and uncertainties in the field of OSA, using novel statistical approaches, and incorporating emerging alternative treatments to CPAP for specific subgroups will keep this field of research challenging.

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Conflicts of interest

The author contributed to several of the discussed studies. There are no other conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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